ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PhotoBarr 15 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15 mg porfimer sodium. After reconstitution, each ml solution contains 2.5 mg porfimer sodium.

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A dark red to reddish brown lyophilised powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Photodynamic therapy (PDT) with PhotoBarr is indicated for ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus (BO).

4.2 Posology and method of administration

Photodynamic therapy with PhotoBarr should be performed only by, or under the supervision of, a physician with experience in endoscopic laser procedures. The medicinal product should only be administered when material and personnel experienced in evaluating and treating anaphylaxis are immediately available.

Posology
The recommended dose of PhotoBarr is 2 mg/kg body weight.

$$\text{Reconstituted PhotoBarr solution (ml)} = \frac{\text{Patient's weight (kg) x 2 mg/kg}}{\text{2.5 mg/ml}} = 0.8 \text{ x patient's weight}$$

After reconstitution, PhotoBarr is a dark red to reddish brown, opaque solution.

Only a solution without particles should be used and without visible signs of deterioration.

Photodynamic therapy with PhotoBarr is a two-stage process requiring administration of both medicinal product and light. One course of PDT consists of one injection plus one or two light applications.

In case of persistence of HGD, further treatment courses (up to a maximum of three courses) may be given (separated by a minimum of 90 days) to increase the response rate. This has to be balanced against the increased rate of stricture formation (see section 4.8 and section 5.1).

Progression to cancer was related to the number of PDT courses administered. Patients who received one course of PDT had a greater risk of progression to cancer than patients who received two or three courses of PDT (50% vs. 39% and 11% respectively)

Method of administration
For instructions on reconstitution prior to administration, see section 6.6.

Physicians should be trained in the use of PDT. The first stage of PDT is the slow intravenous injection of PhotoBarr. The second stage of therapy is illumination with laser light 40-50 hours following injection with PhotoBarr. Patients may receive a second laser light application 96-120 hours after administration.

PhotoBarr should be administered as a single slow intravenous injection over 3 to 5 minutes. If accidentally injected paravenously there may be damage to paravenous tissue. Therefore, care should be taken to prevent extravasation at the injection site. If extravasation does occur, the area should be protected from light for a minimum of 90 days. There is no known benefit from injecting the extravasation site with another substance.

Approximately 40-50 hours after PhotoBarr administration, light should be delivered by a fibre optic diffuser passed through the central channel of a centring balloon. The choice of fibre optic/balloon diffuser combination will depend on the length of oesophagus to be treated (Table 1).

Table 1. Fibre optic diffuser/balloon combination[a]

Treated Barrett's mucosa length (cm)	**Fibre optic diffuser size (cm)**	**Balloon window size (cm)**
6-7	9	7
4-5	7	5
1-3	5	3

[a] Whenever possible, the BO segment selected for treatment should include normal tissue margins of a few millimetres at the proximal and distal ends.

Light doses
Photoactivation is controlled by the total light dose delivered. The objective is to expose and treat all areas of HGD and the entire length of BO. The light dose administered will be 130 Joules/cm (J/cm) of diffuser length using a centring balloon. Based on preclinical studies, acceptable light intensity for the balloon/diffuser combination ranges from 175-270 mW/cm of diffuser.

To calculate the light dose, the following specific light dosimetry equation applies for all fibre optic diffusers:

$$\text{The light dose (J/cm)} = \frac{\text{power output from diffuser (W)} \times \text{treatment time (sec)}}{\text{Diffuser length (cm)}}$$

Table 2 provides the settings that would be used to deliver the dose within the shortest time (light intensity of 270 mW/cm). A second option (light intensity of 200 mW/cm) has also been included where necessary to accommodate lasers with a total capacity that does not exceed 2.5 W.

Table 2. Fibre optic power outputs and treatment times required to deliver 130 J/cm of diffuser length using the centring balloon

Balloon Window Length (cm)	**Diffuser Length (cm)**	**Light Intensity (mW/cm)**	**Required Power Output from Diffuser**[a] **(W)**	**Treatment Time (sec)**	**Treatment Time (min:sec)**
3	5	270	1.35	480	8:00
5	7	270 200	1.90 1.40	480 650	8:00 10:50
7	9	270 200	2.44 1.80	480 650	8:00 10:50

[a] As measured by immersing the diffuser into the cuvette in the power meter and slowly increasing the laser power. Note: No more than 1.5 times the required diffuser power output should be needed from the laser. If more than this is required, the system should be checked.

Short fibre optic diffusers (≤ 2.5 cm) are to be used to pretreat nodules with 50 J/cm diffuser length prior to regular balloon treatment in the first laser light session or for the retreatment of "skip" areas after the first light session. For this treatment, the fibre optic diffuser is used without a balloon, and a light intensity of 400 mW/cm should be used. Table 3 lists appropriate fibre optic power outputs and treatment times using a light intensity of 400 mW/cm.

Table 3. Short fibre optic diffusers to be used without a centering balloon to deliver 50 J/cm of diffuser length at a light intensity of 400 mW/cm

Diffuser length (cm)	Required power output from diffuser[a] (W)	Treatment time (sec)	Treatment time (min:sec)
1.0	0.4	125	2:05
1.5	0.6	125	2:05
2.0	0.8	125	2:05
2.5	1.0	125	2:05

[a]As measured by immersing the diffuser into the cuvette in the power meter and slowly increasing the laser power. Note: No more than 1.5 times the required diffuser power output should be needed from the laser. If more than this is required, the system should be checked.

First light application

A maximum of 7 cm of Barrett's mucosa is treated at the first light session using an appropriate size of centering balloon and fibre optic diffuser (Table 1). Whenever possible, the segment selected for the first light application should include all the areas of HGD. Also, whenever possible, the BO segment selected for the first light applications should include normal tissue margin of a few millimetre at the proximal and distal ends. Nodules are to be pre-treated at a light doses of 50 J/cm of diffuser length with a short (≤ 2.5 cm) fibre optic diffuser placed directly against the nodules followed by standard balloon application as described above.

Repeat light application

A second laser light application may be given to a previously treated segment that shows a 'skip' area, (i.e., an area that does not show sufficient mucosal response) using a short ≤ 2.5 cm fibre optic diffuser at the light dose of 50 J/cm of diffuser length (see Table 3). The treatment regimen is summarized in Table 4. Patients with BO > 7 cm, should have the remaining untreated length of Barrett's epithelium treated with a second PDT course at least 90 days later.

Table 4. High-grade dysplasia in Barrett's oesophagus of ≤ 7 cm

Procedure	Study day	Light delivery Devices	Treatment intent
PhotoBarr Injection	Day 1	NA	Uptake of photosensitiser
Laser Light Application	Day 3[a]	3, 5 or 7 cm balloon (130 J/cm)	Photoactivation
Laser Light Application	Day 5	Short (≤ 2.5 cm) fibre optic diffuser (50 J/cm)	Treatment of "skip" areas only

[a]Discrete nodules will receive an initial light application of 50 J/cm (using short diffuser) before the balloon light application.

Patients may receive a second course of PDT a minimum of 90 days after the initial therapy; up to three courses of PDT (each injection separated by a minimum of 90 days) should be given to a previously treated segment which still shows HGD or to a new segment if the initial Barrett's segment

was >7 cm in length. Both residual and additional segments may be treated in the same light session(s) if the total length of the segments treated with the balloon/diffuser combination is not greater than 7 cm. In the case of a previously treated oesophageal segment, if it has not sufficiently healed and/or histological assessment of biopsies is not clear, the subsequent course of PDT may be delayed for an additional 1-2 months.

Special care to ensure accurate PhotoBarr dosing and/or light dose is crucial, since miscalculation of either medicinal product or light dose may lead to a less effective treatment or cause detrimental effect to the patient. Photodynamic therapy with PhotoBarr should be applied by physicians trained in endoscopic use of PDT and only in those facilities properly equipped for the procedure.

Special populations

Paediatric patients
PhotoBarr is not recommended for use in children below age 18 years due to a lack of data on safety and efficacy.

Elderly patients (≥ 65 years old)
Dose modification based upon age is not required.

Renal impairment
The influence of renal impairment on exposure to porfimer sodium has not been evaluated (see section 4.3).

Hepatic impairment
The influence of hepatic impairment on exposure to porfimer sodium has not been evaluated (see section 4.3 and 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, other porphyrins or to any of the excipients.

Porphyria.

Severe renal and/or hepatic impairment.

Oesophageal or gastric varices or patients with oesophageal ulcers >1 cm in diameter.

Tracheo-oesophageal or broncho-oesophageal fistula.

Suspected erosion of major blood vessels due to risk of massive, potentially fatal haemorrhage.

4.4 Special warnings and precautions for use

Efficacy and especially safety of PDT with PhotoBarr have not been established in patients with contraindications to, or not being eligible for, oesophagectomy. Photodynamic therapy with PhotoBarr has exclusively been studied in patients not suffering from severe medical conditions, such as congestive heart failure of advanced stage or serious pulmonary conditions that might impair the eligibility of patients for surgical procedures.

In clinical trials, PhotoBarr PDT has only been tested in patients being treatment naive concerning mucosal ablative therapy. Safety and efficacy in patients with treatment failure of other local mucosal ablative therapy has not been evaluated.

Elderly
Patients older than 75 years may be at a higher risk of respiratory related adverse events such as pleural effusion and dyspnoea.

Pulmonary or cardiac disorders
Patients with pulmonary or cardiac medical illness or a history of such illness should be treated with caution. These patients may be at higher risk for the development of cardiac and pulmonary related adverse events such as heart rhythm disorders, angina pectoris, dyspnoea, cough, pleural effusion, pharyngitis, atelectasis and events like dehydration (see also section 4.8).

Photosensitivity
All patients who receive PhotoBarr will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, neon lights, etc.) for at least 90 days after treatment, as some patients may remain photosensitive for up to 90 days or more. During this period, patients should wear dark sunglasses, which have an average white light transmittance of < 4% when outdoors. The photosensitivity is due to residual photoactive substances, which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is, however, beneficial because the remaining medicinal product will be inactivated gradually through a photo-bleaching reaction. Therefore, patients should not stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light.
Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If no photosensitivity reaction (erythema, oedema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue exercising precautions for another 2 weeks before retesting.
If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. Conventional UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.

Hepatic impairment
No pharmacokinetic and safety data in patients with hepatic impairment are available. Based on evidence for a primarily hepatic/biliary elimination of photoactive substances, severity of phototoxic reactions and duration of the period of photosensitivity in patients with any grade of hepatic impairment may be increased. PhotoBarr is contraindicated in patients with severe hepatic impairment. Patients with mild to moderate hepatic impairment should be clearly instructed that the period requiring the precautionary measures described below may be longer than 90 days.

Ocular sensitivity
Patients should be advised to consult their ophthalmologist if they notice any vision changes after treatment with PhotoBarr PDT.

Hypersensitivity
Acute hypersensitivity reactions including anaphylaxis have been reported. In case of an allergic reaction, appropriate measures (standard of care) should be taken and the PDT treatment should not be repeated. The medicinal product should only be administered when material and personnel experienced in evaluating and treating anaphylaxis are immediately available.

Non Cardiac Chest Pain
As a result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Oesophageal Stenosis
Prophylactic use of corticosteroids to reduce stricture formation should be avoided during PDT as its use has shown not to reduce, and may worsen, stricture formation.

Nutrition in Patients
PhotoBarr PDT regularly causes dysphagia, odynophagia, nausea and vomiting. Therefore, patients should be advised to receive liquid food during the first days (up to 4 weeks) after the laser light application. If intake of food and/or drink becomes impossible or repeated vomiting occurs, patients should be advised to return to the clinic for evaluation and to receive intravenous fluids if needed.

Use Before or After Radiotherapy
If PDT is to be used before or after radiotherapy, sufficient time should be allowed between the therapies to ensure that the inflammatory reaction produced by the first treatment has subsided prior to commencement of the second treatment.

Thrombo-embolism
There may be an increase in the risk of thrombo-embolic events especially in patients with prolonged immobilization, post major surgery and other thromboembolic risk factors.
Follow-up procedure
Data on the long-term effect of PhotoBarr (beyond two years) are not available at the moment. Also, treating physicians should be aware of the possibility of squamous overgrowth and the risk of overlooking cancer. Therefore, adequate and rigorous surveillance should be continued despite possible endoscopic partial or complete restitution of the normal squamous mucosa. In the clinical studies with PhotoBarr, follow-up surveillance was done every three months, or every six months after four consecutive biopsy results had shown no more high-grade dysplasia (see section 5.1). Available treatment and surveillance guidelines should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed with PhotoBarr investigating pharmacokinetic interactions with other medicinal products.

A study investigating pharmacodynamic interactions has demonstrated that corticosteroids given before or concomitant with PDT to decrease formation of strictures may decrease the safety of treatment.

It is possible that concomitant use of other photosensitising agents (e.g., tetracyclines, sulphonamides, phenothiazines, sulphonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin and fluoroquinolones) could increase the photosensitivity reaction.

PhotoBarr PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischaemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many active substances could influence the effects of PDT, possible examples of which are described below. There are no human data available to support or rebut these possibilities. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulphoxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischaemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PhotoBarr PDT. Medicinal products that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT.

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no clinical data on exposed pregnancies available for porfimer sodium. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Porfimer sodium should not be used during pregnancy, unless clearly necessary. Women of child-bearing potential should use effective contraception before, during and for at least 90 days after treatment.

Lactation
It is not known whether porfimer sodium is excreted into human breast milk. In rats, porfimer sodium passed into breast milk. Breast-feeding should be terminated prior to treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
For the PDT procedure, sedation may be required, and consequently caution should be taken. Patients should not drive or use machines after the light treatment if they have been sedated for the procedure.

4.8 Undesirable effects

a. Summary of the safety profile

All patients who receive PhotoBarr will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see section 4.4). In an open label pharmacokinetic study, all 24 healthy subjects experienced photosensitivity reactions, which were characteristically represented by erythematous rash and oedema and were mild to moderate in intensity. The photosensitivity reactions occurred primarily on the face, hands, and neck regions, which are the areas of the skin that are most susceptible to accidental sunlight exposure. Other less common skin manifestations were reported in areas where photosensitivity reactions had occurred, such as increased hair growth, skin discolouration, skin nodules, skin wrinkling and skin fragility. These manifestations may be attributable to a pseudoporphyria state (temporary medicinal product-induced cutaneous porphyria). The frequency and nature of the photosensitivity reactions experienced in this study are unlike the documented incidence seen in previous clinical studies in cancer patients (approx. 20%) or the spontaneously reported incidence from commercial use of PhotoBarr (< 20%). It is possible that prolonged exposure to light at the clinical research unit or accidental sunlight exposure after discharge may be responsible for the high frequency of photosensitivity reactions. The more active lifestyle of the healthy and relatively younger subjects compared with cancer patients may have been a contributing factor to these photosensitivity reactions.

PhotoBarr PDT plus omeprazole (PDT + OM) treatment was compared to a group treated with omeprazole alone (OM only), in the BO with HGD controlled clinical trial. In the PDT + OM group, 133 patients were treated. The most frequently reported adverse reactions were photosensitivity reactions (69%), oesophageal stenosis (40%), vomiting (32%), chest pain of non-cardiac origin (20%), pyrexia (20%), dysphagia (19%), constipation (13%), dehydration (12%) and nausea (11%). The majority of these reported adverse reactions were mild to moderate in intensity.

b.Tabulated summary of adverse reactions

Adverse reactions reported are listed below in Table 5 by organ class and frequency. Frequencies are defined as: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5. Summary of adverse reactions with porfimer sodium

Infections and infestations	
Uncommon:	Bronchitis, nail fungal infection, sinusitis, skin infection
Not known:	Pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Uncommon:	Basal cell carcinoma, lentigo
Blood and lymphatic system disorders	
Uncommon:	Leukocytosis
Not known:	Anaemia
Immune system disorders	
Not known:	Hypersensitivity
Metabolism and nutrition disorders	
Very common:	Dehydration*
Common:	Appetite decreased, electrolyte imbalance
Uncommon:	Hypokalaemia
Psychiatric disorders	
Common:	Anxiety, insomnia
Uncommon:	Restlessness
Nervous system disorders	
Common:	Headache, paraesthesia, dysgeusia
Uncommon:	Dizziness, hypoaesthesia, tremor
Eye disorders	
Uncommon:	Eye irritation, eye oedema
Not known:	Cataract
Ear and labyrinth disorders	
Uncommon:	Deafness, tinnitus, tinnitus aggravated
Cardiac disorders	
Common:	Tachycardia, chest pain
Uncommon:	Angina pectoris, atrial fibrillation, atrial flutter, chest discomfort
Vascular disorders	
Uncommon:	Hypertension, haemorrhage, hot flushes, hypotension, orthostatic hypotension
Not known:	Embolism, Deep vein thrombosis, Phlebitis
Respiratory, thoracic and mediastinal disorders	
Common:	Pleural effusion, pharyngitis, atelectasis, dyspnoea
Uncommon:	Choking, dyspnoea exertional, haemoptysis, hypoxia, nasal congestion, pneumonia aspiration, productive cough, respiratory depression, respiratory tract congestion, wheezing
Gastrointestinal disorders	
Very common:	Oesophageal stenosis acquired*, vomiting*, dysphagia, constipation, nausea*
Common:	Hiccups, odynophagia, diarrhoea, dyspepsia, oesophageal ulcer, abdominal pain upper*, abdominal pain, haematemesis, oesophageal pain, eructation, melaena (haematocheznia), oesophageal disorder, regurgitation of food, abdominal rigidity, oesophageal spasm, oesophagitis.
Uncommon:	Loose stools, oesophagitis ulcerative, abdominal discomfort, abdominal distension, abdominal pain lower, acquired pylori stenosis, chapped lips, colitis, flatulence, gastritis, gastrointestinal haemorrhage, halitosis, oesophageal haemorrhage, oesophageal perforation.
Not known:	Tracheo-oesophageal fistula, Gastrointestinal necrosis
Skin and subcutaneous tissue disorders	

Very common:	Photosensitivity reaction
Common:	Pruritus, rash, skin fragility, skin discolouration, skin ulcer, dermatitis exfoliative, dry skin, milia, rash maculo-papular, rash papular, scar, skin hyperpigmentation, skin lesion, skin nodule, urticaria
Uncommon:	Cold sweat, dermatitis, hair growth abnormal, increased tendency to bruise, keloid scar, night sweats, photosensitive rash, rash macular, rash scaly, scab, scar pain, vitiligo.
Musculoskeletal and connective tissue disorders	
Common:	Back pain, pain in the limb
Uncommon:	Joint contracture, joint range of motion decreased, musculoskeletal chest pain, plantar fascitis
Renal and urinary disorders:	
Uncommon:	Urinary retention
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia
Congenital, and familial and genetic disorders	
Uncommon:	Pigmented naevus
General disorders and administration site conditions	
Very common:	Pyrexia
Common:	Rigors, fatigue
Uncommon:	Feeling hot, injection site erythema, lethargy, malaise, oedema peripheral, pain, pitting oedema, temperature intolerance, weakness
Investigations	
Common:	Weight decreased, body temperature increased
Uncommon:	Blood albumin decreased, blood chloride increased, blood urea increased, haematocrit decreased, haemoglobin decreased, oxygen saturation decreased, protein total decreased
Injury poisoning, and procedural complications	
Common:	Post procedural pain, abrasion
Uncommon:	Blister, post procedural haemorrhage

* see section c.

c. Description of selected adverse reactions

Of the serious adverse events (SAEs) in the PhotoBarr PDT + OM group, 44 (23.1%) were considered associated with the treatment. The most frequently reported treatment-associated serious adverse reaction (SAR) was dehydration (4%), experienced by 5 patients. The majority of the SARs were gastrointestinal disorders (8% - 11 patients), specifically nausea (3% - 4 patients), vomiting (3% - 4 patients) and upper abdominal pain (2% - 2 patients).

The majority of treatment-associated oesophageal stenosis (which includes oesophageal narrowing and oesophageal strictures) reported in the PhotoBarr PDT + OM group were of mild or moderate intensity (92%). All incidences of strictures were considered associated with treatment of which 1% was considered serious.

An occurrence rate of 12% for oesophageal strictures was observed during the first course of treatment. The occurrence rate rose to 32% when a second course of therapy was given, especially in the areas where second treatment overlaps the first and amounted to 10% for those who received a third treatment course. The majority of these was mild to moderate in intensity and could be managed through 1-2 dilatations. Eight percent were severe, requiring multiple (6 - >10) dilatations. The formation of oesophageal stenosis cannot be reduced or eliminated by the use of steroids.

4.9 Overdose

PhotoBarr
There is no information on overdose of PhotoBarr. The recommended 2 mg/kg dose, instead of the recommended single administration, was given twice two days apart (10 patients) and three times within two weeks (1 patient), without any notable adverse reactions being reported. The effects of an overdose on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of PhotoBarr is administered. In the event of an overdose, patients should protect their eyes and skin from direct sunlight or bright indoor lights for 90 days. At this time, patients should test for residual photosensitivity (see section 4.4).
Porfimer sodium is not dialyzable.

Laser light
Light doses of two to three times the recommended dose have been administered to a few patients with superficial endobronchial tumours. One patient experienced life-threatening dyspnoea and the others had no notable complications. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensitizers used in photodynamic/radiation therapy, ATC code: L01XD01

Mechanism of action
Porfimer sodium is a mixture of porphyrin units, which are linked together in chains of two to eight units The cytotoxic actions of porfimer sodium are light and oxygen-dependent. Photodynamic therapy with PhotoBarr is a 2-stage process. The first stage is the intravenous injection of PhotoBarr. Clearance from a variety of tissues occurs over 40-72 hours, but tumours, skin, and organs of the reticuloendothelial system (including liver and spleen) retain porfimer sodium for a longer period. Illumination of the target area with 630 nm wavelength laser light constitutes the second stage of therapy. Tumour and dysplastic tissue selectivity in treatment may occur partly through selective retention of porfimer sodium but mainly through a selective delivery of light. Cellular damage caused by porfimer sodium PDT is a consequence of the propagation of free radical reactions. Radical initiation may occur after porfimer sodium absorbs light to form a porphyrin excited state. Spin transfer from porfimer sodium to molecular oxygen may then generate singlet oxygen. Subsequent free radical reactions can form superoxide and hydroxyl radicals. Tumour cell death also occurs through ischaemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A_2 release. The laser treatment induces a photochemical, not a thermal, effect. The necrotic reaction and associated inflammatory response evolve over several days.

Clinical efficacy
In a controlled clinical trial, a PhotoBarr PDT + OM (omeprazole) patient group (n=183)was compared to a group of patients receiving OM only (n=70). Eligible patients for this study were to have biopsy-proven HGD in Barrett's oesophagus (BO). Patients were excluded from the study if there was a presence of invasive oesophageal cancer, if they had a history of cancer other than non-melanoma skin cancer or if they had received prior PDT to the oesophagus. Other exclusion criteria were patients in whom omeprazole therapy was contraindicated.

Patients randomised to treatment with PDT received PhotoBarr at a dose of 2 mg/kg body weight through slow intravenous injection over 3 to 5 minutes. One or 2 laser light treatments were administered following PhotoBarr injection. The first laser light session occurred 40-50 hours after injection and a second session, if indicated, occurred 96-120 hours after injection. Co-administration of omeprazole (20 mg BID) began at least 2 days before PhotoBarr injection. Patients randomised to the OM only group received orally omeprazole 20 mg BID for the duration of the study.

Patients were followed every 3 months until 4 consecutive, quarterly follow-up endoscopic biopsy results were negative for HGD, and then biannually until the last enrolled patient had completed a minimum of 24 months of follow-up evaluations after randomisation.

PhotoBarr PDT + OM was effective in eliminating HGD in patients with BO. At final analysis, performed at a minimum of 24 months follow-up, a statistically significant percentage of patients (77%) in the PhotoBarr PDT + OM group demonstrated complete HGD ablation compared to 39% of patients in the OM alone group ($p<0.0001$). Fifty-two percent of patients in the PDT + OM group showed normal squamous cell epithelium while 59% had absence of dysplasia compared to 7% and 14% in the OM alone group, respectively ($p<0.0001$). These results confirm those observed after a minimum of 6 months follow-up which showed HGD ablation in 72% of patients in the PhotoBarr PDT + OM group compared to 31% in the OM only group. Forty-one percent of patients showed normal squamous cell epithelium and 49% had absence of dysplasia.

By the end of the minimum follow-up of two years, 13% in the PhotoBarr PDT + OM group had progressed to cancer compared to 28% in the OM only group in the intent-to-treat (ITT) population. The proportion of patients who progressed to cancer in the PhotoBarr PDT + OM group was statistically lower than in the OM only group ($p=0.0060$). The survival curves indicated that, by the end of the entire follow-up period, patients in the PhotoBarr PDT + OM group had a 83% chance of being cancer-free as compared to a 53% chance for patients in the OM only group. Comparison between the survival curves of the two treatment arms using the log rank test showed a statistically significant difference between the curves of the two groups in the ITT population ($p=0.0014$), indicating a significant delay in the progression to cancer.

5.2 Pharmacokinetic properties

The pharmacokinetics of porfimer sodium have been studied in 12 patients with endobronchial cancer and 23 healthy subjects (11 men and 12 women), given 2 mg/kg porfimer sodium through slow intravenous injection. Plasma samples were obtained out to 56 days (patients) or 36 days (volunteers) post-injection.

In patients, the mean peak plasma concentration (C_{max}) was 79.6 µg/ml (CV 61%, range 39-222), whereas in volunteers C_{max} was 40 µg/ml and AUC_{inf} was 2400 µg/h/ml.

Distribution
In vitro binding of porfimer sodium to human serum protein is around 90% and independent of concentration between 20 and 100 µg/ml.

Elimination
Porfimer sodium is cleared slowly from the body, with a mean CL_T of 0.859 ml/h/kg (CV 53%) in patients. The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The mean elimination half-life ($t_{1/2}$) was 21.5 days (CV 26 %, range 264-672) in patients and 17 days in volunteers.

Special populations
The influence of renal and hepatic impairment on exposure to porfimer sodium has not been evaluated (see sections 4.2, 4.3 and 4.4).

Gender had no effect on pharmacokinetic parameters except for t_{max}, which was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of porfimer sodium in men and women were very similar.

5.3 Preclinical safety data

Porfimer sodium was not mutagenic in standard genotoxicity tests in the absence of light. With light activation, porfimer sodium was mutagenic in some *in-vitro* tests.

Reproductive toxicology studies were insufficient to support the safety of porfimer sodium during pregnancy, as no light activation had been used. In these studies foetotoxicity, but not teratogenicity, occurred in rats and rabbits only at evaluated intravenous doses (greater than of equal to 4 mg/kg) and at greater frequency (daily) compared in the clinical use.

Preclinical studies indicate that the excretion of porfimer sodium components occurs primarily via the faecal route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder: 3 years.

After reconstitution: use immediately (within 3 hours).

After it has been reconstituted, PhotoBarr should be used immediately (within 3 hours) and protected from light. Chemical and physical in-use stability has been demonstrated for 3 hours at 23°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton and vial after EXP.

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

15 mg powder in a vial (glass type I, 7 ml capacity) with a grey butyl stopper.
Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution
PhotoBarr 15 mg vial should be reconstituted with 6.6 ml of 5% glucose solution for injection resulting in a final porfimer sodium concentration of 2.5 mg/ml in the solution for injection.

Do not use other diluents. Do not mix PhotoBarr with other medicinal products in the same solution.

Sufficient vials of PhotoBarr should be reconstituted to provide the patient with a dose of 2 mg/kg. For most patients (up to 75 kg) two vials of PhotoBarr 75 mg will suffice. A PhotoBarr 15 mg vial will be needed for every additional 7.5 kg body weight.

Spills and disposal
Spills of PhotoBarr should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended.
PhotoBarr is for single use only and any unused solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

Accidental exposure
PhotoBarr is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, PhotoBarr might be an eye and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic overdose, any accidentally overexposed person must be protected from bright light.'

7. MARKETING AUTHORISATION HOLDER

Pinnacle Biologics B.V.
p/a Trust Company Amsterdam B.V.
Crystal Tower 21st Floor,
Orlyplein 10, 1043 DP Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/272/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 March 2004
Date of latest renewal: 4 March 2009

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PhotoBarr 75 mg powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 75 mg porfimer sodium. After reconstitution, each ml solution contains 2.5 mg porfimer sodium.

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A dark red to reddish brown lyophilised powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Photodynamic therapy (PDT) with PhotoBarr is indicated for:

- ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus (BO).

4.2 Posology and method of administration

Photodynamic therapy with PhotoBarr should be performed only by, or under the supervision of, a physician with experience in endoscopic laser procedures. The medicinal product should only be administered when material and personnel experienced in evaluating and treating anaphylaxis are immediately available.

Posology
The recommended dose of PhotoBarr is 2 mg/kg body weight.

$$\text{Reconstituted PhotoBarr solution (ml)} = \frac{\text{Patient's weight (kg) x 2 mg/kg}}{\text{2.5 mg/ml}} = 0.8 \text{ x patient's weight}$$

After reconstitution, PhotoBarr is a dark red to reddish brown, opaque solution.

Only a solution without particles should be used and without visible signs of deterioration.

Photodynamic therapy with PhotoBarr is a two-stage process requiring administration of both medicinal product and light. One course of PDT consists of one injection plus one or two light applications.

In case of persistence of HGD, further treatment courses (up to a maximum of three courses) may be given (separated by a minimum of 90 days) to increase the response rate. This has to be balanced against the increased rate of stricture formation (see section 4.8 and section 5.1).

Progression to cancer was related to the number of PDT courses administered. Patients who received one course of PDT had a greater risk of progression to cancer than patients who received two or three courses of PDT (50% vs. 39% and 11% respectively)

Method of administration
For instructions on reconstitution prior to administration, see section 6.6

Physicians should be trained in the use of PDT. The first stage of PDT is the slow intravenous injection of PhotoBarr. The second stage of therapy is illumination with laser light 40-50 hours following injection with PhotoBarr. Patients may receive a second laser light application 96-120 hours after administration.

PhotoBarr should be administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. If accidentally injected paravenously there may be damage to paravenous tissue. Therefore, care should be taken to prevent extravasation at the injection site. If extravasation does occur, the area should be protected from light for a minimum of 90 days. There is no known benefit from injecting the extravasation site with another substance.

Approximately 40-50 hours after PhotoBarr administration, light should be delivered by a fibre optic diffuser passed through the central channel of a centring balloon. The choice of fibre optic/balloon diffuser combination will depend on the length of oesophagus to be treated (Table 1).

Table 1. Fibre optic diffuser/balloon combination[a]

Treated Barrett's Mucosa Length (cm)	**Fibre Optic Diffuser Size (cm)**	**Balloon Window Size (cm)**
6-7	9	7
4-5	7	5
1-3	5	3

[a] Whenever possible, the BO segment selected for treatment should include normal tissue margins of a few millimetres at the proximal and distal ends.

Light doses
Photoactivation is controlled by the total light dose delivered. The objective is to expose and treat all areas of HGD and the entire length of BO. The light dose administered will be 130 Joules/cm (J/cm) of diffuser length using a centring balloon. Based on preclinical studies, acceptable light intensity for the balloon/diffuser combination ranges from 175-270 mW/cm of diffuser.

To calculate the light dose, the following specific light dosimetry equation applies for all fibre optic diffusers:

$$\text{The light dose (J/cm)} = \frac{\text{power output from diffuser (W)} \times \text{treatment time (sec)}}{\text{Diffuser length (cm)}}$$

Table 2 provides the settings that would be used to deliver the dose within the shortest time (light intensity of 270 mW/cm). A second option (light intensity of 200 mW/cm) has also been included where necessary to accommodate lasers with a total capacity that does not exceed 2.5 W.

Table 2. Fibre optic power outputs and treatment times required to deliver 130 J/cm of diffuser length using the centring balloon

Balloon window length (cm)	**Diffuser length (cm)**	**Light intensity (mW/cm)**	**Required power output from diffuser[a] (W)**	**Treatment time (sec)**	**Treatment time (min:sec)**
3	5	270	1.35	480	8:00

5	7	270 200	1.90 1.40	480 650	8:00 10:50
7	9	270 200	2.44 1.80	480 650	8:00 10:50

[a] As measured by immersing the diffuser into the cuvette in the power meter and slowly increasing the laser power. Note: No more than 1.5 times the required diffuser power output should be needed from the laser. If more than this is required, the system should be checked.

Short fibre optic diffusers (≤ 2.5 cm) are to be used to pretreat nodules with 50 J/cm diffuser length prior to regular balloon treatment in the first laser light session or for the retreatment of "skip" areas after the first light session. For this treatment, the fibre optic diffuser is used without a balloon, and a light intensity of 400 mW/cm should be used. Table 3 lists appropriate fibre optic power outputs and treatment times using a light intensity of 400 mW/cm.

Table 3. Short fibre optic diffusers to be used without a centering balloon to deliver 50 J/cm of diffuser length at a light intensity of 400 mW/cm

Diffuser length (cm)	Required power output from diffuser[a] (W)	Treatment time (sec)	Treatment time (min:sec)
1.0	0.4	125	2:05
1.5	0.6	125	2:05
2.0	0.8	125	2:05
2.5	1.0	125	2:05

[a]As measured by immersing the diffuser into the cuvette in the power meter and slowly increasing the laser power. Note: No more than 1.5 times the required diffuser power output should be needed from the laser. If more than this is required, the system should be checked.

First light application

A maximum of 7 cm of Barrett's mucosa is treated at the first light session using an appropriate size of centering balloon and fibre optic diffuser (Table 1). Whenever possible, the segment selected for the first light application should include all the areas of HGD. Also, whenever possible, the BO segment selected for the first light applications should include normal tissue margin of a few millimetre at the proximal and distal ends. Nodules are to be pre-treated at a light doses of 50 J/cm of diffuser length with a short (≤ 2.5 cm) fibre optic diffuser placed directly against the nodules followed by standard balloon application as described above.

Repeat light application

A second laser light application may be given to a previously treated segment that shows a 'skip' area, (i.e., an area that does not show sufficient mucosal response) using a short ≤ 2.5 cm fibre optic diffuser at the light dose of 50 J/cm of diffuser length (see Table 3). The treatment regimen is summarized in Table 4. Patients with BO > 7 cm, should have the remaining untreated length of Barrett's epithelium treated with a second PDT course at least 90 days later.

Table 4. High-grade dysplasia in Barrett's oesophagus of < 7 cm

Procedure	Study day	Light delivery devices	Treatment intent
PhotoBarr Injection	Day 1	NA	Uptake of photosensitiser
Laser Light Application	Day 3[a]	3, 5 or 7 cm balloon (130 J/cm)	Photoactivation
Laser Light Application	Day 5	Short (≤ 2.5 cm) fibre optic diffuser (50 J/cm)	Treatment of "skip" areas only

[a]Discrete nodules will receive an initial light application of 50 J/cm (using short diffuser) before the balloon light application.

Patients may receive a second course of PDT a minimum of 90 days after the initial therapy; up to three courses of PDT (each injection separated by a minimum of 90 days) should be given to a previously treated segment which still shows HGD or to a new segment if the initial Barrett's segment was >7 cm in length. Both residual and additional segments may be treated in the same light session(s) if the total length of the segments treated with the balloon/diffuser combination is not greater than 7 cm. In the case of a previously treated oesophageal segment, if it has not sufficiently healed and/or histological assessment of biopsies is not clear, the subsequent course of PDT may be delayed for an additional 1-2 months.

Special care to ensure accurate PhotoBarr dosing and/or light dose is crucial, since miscalculation of either medicinal product or light dose may lead to a less effective treatment or cause detrimental effect to the patient. Photodynamic therapy with PhotoBarr should be applied by physicians trained in endoscopic use of PDT and only in those facilities properly equipped for the procedure.

Special populations

Paediatric patients
PhotoBarr is not recommended for use in children below age 18 years due to a lack of data on safety and efficacy.

Elderly patients(≥ 65 years old)
Dose modification based upon age is not required.

Renal impairment
The influence of renal impairment on exposure to porfimer sodium has not been evaluated. (see section 4.3).

Hepatic impairment
The influence of hepatic impairment on exposure to porfimer sodium has not been evaluated (see section 4.3 and 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance, other porphyrins or to any of the excipients.
- Porphyria.
- Severe renal and/or hepatic impairment.
- Oesophageal or gastric varices or patients with oesophageal ulcers >1 cm in diameter.
- Tracheo-oesophageal or broncho-oesophageal fistula.
- Suspected erosion of major blood vessels due to risk of massive, potentially fatal haemorrhage.

4.4 Special warnings and precautions for use

Efficacy and especially safety of PDT with PhotoBarr have not been established in patients with contraindications to, or not being eligible for, oesophagectomy. Photodynamic therapy with PhotoBarr has exclusively been studied in patients not suffering from severe medical conditions, such as congestive heart failure of advanced stage or serious pulmonary conditions that might impair the eligibility of patients for surgical procedures.

In clinical trials, PhotoBarr PDT has only been tested in patients being treatment naive concerning mucosal ablative therapy. Safety and efficacy in patients with treatment failure of other local mucosal ablative therapy has not been evaluated.

Elderly
Patients older than 75 years may be at a higher risk of respiratory related adverse events such as pleural effusion and dyspnoea

Pulmonary or cardiac disorders
Patients with pulmonary or cardiac medical illness or a history of such illness should be treated with caution. These patients may be at higher risk for the development of cardiac and pulmonary related adverse events such as heart rhythm disorders, angina pectoris, dyspnoea, cough, pleural effusion, pharyngitis, atelectasis and events like dehydration (see also section 4.8).

Photosensitivity
All patients who receive PhotoBarr will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, neon lights, etc.) for at least 90 days after treatment as some patients may remain photosensitive for up to 90 days or more. During this period, patients should wear dark sunglasses, which have an average white light transmittance of <4% when outdoors. The photosensitivity is due to residual photoactive substances, which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is, however, beneficial because the remaining medicinal product will be inactivated gradually through a photo-bleaching reaction. Therefore, patients should not stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If no photosensitivity reaction (erythema, oedema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue exercising precautions for another 2 weeks before retesting. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. Conventional UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.

Hepatic Impairment
No pharmacokinetic and safety data in patients with hepatic impairment are available. Based on evidence for a primarily hepatic/biliary elimination of photoactive substances, severity of phototoxic reactions and duration of the period of photosensitivity in patients with any grade of hepatic impairment may be increased. PhotoBarr is contraindicated in patients with severe hepatic impairment. Patients with mild to moderate hepatic impairment should be clearly instructed that the period requiring the precautionary measures described below may be longer than 90 days.

Ocular sensitivity
Patients should be advised to consult their ophthalmologist if they notice any vision changes after treatment with PhotoBarr PDT.

Hypersensitivity
Acute hypersensitivity reactions including anaphylaxis have been reported. In case of an allergic reaction, appropriate measures (standard of care) should be taken and the PDT treatment should not be repeated. The medicinal product should only be administered when material and personnel experienced in evaluating and treating anaphylaxis are immediately available.

Non Cardiac Chest Pain
As a result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Oesophageal Stenosis
Prophylactic use of corticosteroids to reduce stricture formation should be avoided during PDT as its use has shown not to reduce, and may worsen, stricture formation.

Nutrition in Patients
PhotoBarr PDT regularly causes dysphagia, odynophagia, nausea and vomiting. Therefore, patients should be advised to receive liquid food during the first days (up to 4 weeks) after the laser light application. If intake of food and/or drink becomes impossible or repeated vomiting occurs, patients should be advised to return to the clinic for evaluation and to receive intravenous fluids if needed.

Use Before or After Radiotherapy
If PDT is to be used before or after radiotherapy, sufficient time should be allowed between the therapies to ensure that the inflammatory reaction produced by the first treatment has subsided prior to commencement of the second treatment.

Thrombo-embolism
There may be an increase in the risk of thrombo-embolic events especially in patients with prolonged immobilization, post major surgery and other thromboembolic risk factors.

Follow-up procedure
Data on the long-term effect of PhotoBarr (beyond two years) are not available at the moment. Also, treating physicians should be aware of the possibility of squamous overgrowth and the risk of overlooking cancer.

Therefore, adequate and rigorous surveillance should be continued despite possible endoscopic partial or complete restitution of the normal squamous mucosa.

In the clinical studies with PhotoBarr, follow-up surveillance was done every three months, or every six months after four consecutive biopsy results had shown no more high-grade dysplasia (see section 5.1).
Available treatment and surveillance guidelines should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed with PhotoBarr investigating pharmacokinetic product interactions with other medicinal products.

A study investigating pharmacodynamic interactions has demonstrated that corticosteroids given before or concomitant with PDT to decrease formation of strictures may decrease the safety of treatment.

It is possible that concomitant use of other photosensitising agents (e.g., tetracyclines, sulphonamides, phenothiazines, sulphonylurea hypoglycaemic agents, thiazide diuretics, griseofulvin and fluoroquinolones) could increase the photosensitivity reaction.

PhotoBarr PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischaemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many active substances could influence the effects of PDT, possible

examples of which are described below. There are no human data available to support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulphoxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischaemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PhotoBarr PDT. Medicinal products that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT.

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no clinical data on exposed pregnancies available for porfimer sodium. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Porfimer sodium should not be used during pregnancy unless clearly necessary.
Women of child-bearing potential should use effective contraception before, during and for at least 90 days after treatment.

Lactation
It is not known whether porfimer sodium is excreted into human breast milk. In rats porfimer sodium passed into breast milk. Breastfeeding should be terminated prior to treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
For the PDT procedure, sedation may be required and consequently caution should be taken. Patients should not drive or use machines after the light treatment if they have been sedated for the procedure.

4.8 Undesirable effects

a. Summary of safety profile

All patients who receive PhotoBarr will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see section 4.4). In an open label pharmacokinetic study, all 24 healthy subjects experienced photosensitivity reactions, which were characteristically represented by erythematous rash and oedema and were mild to moderate in intensity. The photosensitivity reactions occurred primarily on the face, hands, and neck regions, which are the areas of the skin that are most susceptible to accidental sunlight exposure. Other less common skin manifestations were reported in areas where photosensitivity reactions had occurred, such as increased hair growth, skin discolouration, skin nodules, skin wrinkling and skin fragility. These manifestations may be attributable to a pseudoporphyria state (temporary medicinal product-induced cutaneous porphyria). The frequency and nature of the photosensitivity reactions experienced in this study are unlike the documented incidence seen in previous clinical studies in cancer patients (approx. 20%) or the spontaneously reported incidence from commercial use of PhotoBarr (< 20%). It is possible that prolonged exposure to light at the clinical research unit or accidental sunlight exposure after discharge may be responsible for the high frequency of photosensitivity reactions. The more active lifestyle of the healthy and relatively younger subjects compared with cancer patients may have been a contributing factor to these photosensitivity reactions.

PhotoBarr PDT plus omeprazole (PDT + OM) treatment was compared to a group treated with omeprazole alone (OM only), in the BO with HGD controlled clinical trial. In the PDT + OM group, 133 patients were treated. The most frequently reported adverse reactions were photosensitivity reactions (69%), oesophageal stenosis (40%), vomiting (32%), chest pain of non-cardiac origin (20%),

pyrexia (20%), dysphagia (19%), constipation (13%), dehydration (12%) and nausea (11%). The majority of these reported adverse reactions were mild to moderate in intensity.

b Tabulated summary of adverse events
Adverse reactions reported are listed below in Table 5 by organ class and frequency. Frequencies are defined as: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5. Summary of adverse reactions with porfimer sodium

Infections and infestations	
Uncommon:	Bronchitis, nail fungal infection, sinusitis, skin infection
Not known:	Pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Uncommon:	Basal cell carcinoma, lentigo
Blood and the lymphatic system disorders	
Uncommon:	Leukocytosis
Not known:	Anaemia
Immune system disorders	
Not known:	Hypersensitivity
Metabolism and nutrition disorders	
Very common:	Dehydration*
Common:	Appetite decreased, electrolyte imbalance
Uncommon:	Hypokalaemia
Psychiatric disorders	
Common:	Anxiety, insomnia
Uncommon:	Restlessness
Nervous system disorders	
Common:	Headache, paraesthesia, dysgeusia
Uncommon:	Dizziness, hypoaesthesia, tremor
Eye disorders	
Uncommon:	Eye irritation, eye oedema
Not known:	Cataract
Ear and labyrinth disorders	
Uncommon:	Deafness, tinnitus, tinnitus aggravated
Cardiac disorders	
Common:	Tachycardia, chest pain
Uncommon:	Angina pectoris, atrial fibrillation, atrial flutter, chest discomfort
Vascular disorders	
Uncommon:	Hypertension, haemorrhage, hot flushes, hypotension, orthostatic hypotension
Not known:	Embolism, Deep vein thrombosis, Phlebitis
Respiratory, thoracic and mediastinal disorders	
Common:	Pleural effusion, pharyngitis, atelectasis, dyspnoea
Uncommon:	Choking, dyspnoea exertional, haemoptysis, hypoxia, nasal congestion, pneumonia aspiration, productive cough, respiratory depression, respiratory tract congestion, wheezing

Gastrointestinal disorders	
Very common:	Oesophageal stenosis acquired*, vomiting*, dysphagia, constipation, nausea*
Common:	Hiccups, odynophagia, diarrhoea, dyspepsia, oesophageal ulcer, abdominal pain upper*, abdominal pain, haematemesis, oesophageal pain, eructation, melaena (haematocheznia), oesophageal disorder, regurgitation of food, abdominal rigidity, oesophageal spasm, oesophagitis.
Uncommon:	Loose stools, oesophagitis ulcerative, abdominal discomfort, abdominal distension, abdominal pain lower, acquired pylori stenosis, chapped lips, colitis, flatulence, gastritis, gastrointestinal haemorrhage, halitosis, oesophageal haemorrhage, oesophageal perforation.
Not known:	Tracheo-oesophageal fistula, Gastrointestinal necrosis
Skin and subcutaneous tissue disorders	
Very common:	Photosensitivity reaction
Common:	Pruritus, rash, skin fragility, skin discolouration, skin ulcer, dermatitis exfoliative, dry skin, milia, rash maculo-papular, rash papular, scar, skin hyperpigmentation, skin lesion, skin nodule, urticaria
Uncommon:	Cold sweat, dermatitis, hair growth abnormal, increased tendency to bruise, keloid scar, night sweats, photosensitive rash, rash macular, rash scaly, scab, scar pain, vitiligo.
Musculoskeletal and connective tissue disorders	
Common:	Back pain, pain in the limb
Uncommon:	Joint contracture, joint range of motion decreased, musculoskeletal chest pain, plantar fascitis
Renal and urinary disorders:	
Uncommon:	Urinary retention
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia
Congenital and familial and genetic disorders	
Uncommon:	Pigmented naevus
General disorders and administration site conditions	
Very common:	Pyrexia
Common:	Rigors, fatigue
Uncommon:	Feeling hot, injection site erythema, lethargy, malaise, oedema peripheral, pain, pitting oedema, temperature intolerance, weakness
Investigations	
Common:	Weight decreased, body temperature increased
Uncommon:	Blood albumin decreased, blood chloride increased, blood urea increased, haematocrit decreased, haemoglobin decreased, oxygen saturation decreased, protein total decreased
Injury, poisoning, and procedural complications	
Common:	Post procedural pain, abrasion
Uncommon:	Blister, post procedural haemorrhage

* see section c.

c. Description of selected adverse reactions

Of the serious adverse events (SAEs) in the PhotoBarr PDT + OM group, 44 (23.1%) were considered associated with the treatment. The most frequently reported treatment-associated serious adverse reaction (SAR) was dehydration (4%), experienced by 5 patients. The majority of the SAEs experienced were gastrointestinal disorders (8% - 11 patients), specifically nausea (3% - 4 patients), vomiting (3% - 4 patients) and upper abdominal pain (2% - 2 patients).

The majority of treatment-associated oesophageal stenosis (which includes oesophageal narrowing and oesophageal strictures) reported in the PhotoBarr PDT + OM group were of mild or moderate intensity (92%). All incidences of strictures were considered associated with treatment of which 1% was considered serious.

An occurrence rate of 12% for oesophageal strictures was observed during the first course of treatment. The occurrence rate rose to 32% when a second course of therapy was given, especially in the areas where second treatment overlaps the first and amounted to 10% for those who received a third treatment course. The majority of these was mild to moderate in intensity and could be managed through 1-2 dilatations. Eight percent were severe, requiring multiple (6 - >10) dilatations. The formation of oesophageal stenosis cannot be reduced or eliminated by the use of steroids.

4.9 Overdose

PhotoBarr
There is no information on overdose of PhotoBarr. The recommended 2 mg/kg dose, instead of the recommended single administration, was given twice two days apart (10 patients) and three times within two weeks (1 patient) without any notable adverse reactions being reported. The effects of an overdose on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of PhotoBarr is administered. In the event of an overdose, patients should protect their eyes and skin from direct sunlight or bright indoor lights for 90 days. At this time, patients should test for residual photosensitivity (see section 4.4). Porfimer sodium is not dialyzable.

Laser light
Light doses of two to three times the recommended dose have been administered to a few patients with superficial endobronchial tumours. One patient experienced life-threatening dyspnoea and the others had no notable complications. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensitizers used in photodynamic/radiation therapy, ATC code: L01XD01

Mechanism of action
Porfimer sodium is a mixture of porphyrin units, which are linked together in chains of two to eight units. The cytotoxic actions of porfimer sodium are light and oxygen-dependent. Photodynamic therapy with PhotoBarr is a 2-stage process. The first stage is the intravenous injection of PhotoBarr. Clearance from a variety of tissues occurs over 40-72 hours, but tumours, skin, and organs of the reticuloendothelial system (including liver and spleen) retain porfimer sodium for a longer period. Illumination of the target area with 630 nm wavelength laser light constitutes the second stage of therapy. Tumour and dysplastic tissue selectivity in treatment may occur partly through selective retention of porfimer sodium but mainly through a selective delivery of light. Cellular damage caused by porfimer sodium PDT is a consequence of the propagation of free radical reactions. Radical initiation may occur after porfimer sodium absorbs light to form a porphyrin excited state. Spin transfer from porfimer sodium to molecular oxygen may then generate singlet oxygen. Subsequent free radical reactions can form superoxide and hydroxyl radicals. Tumour cell death also occurs through ischaemic necrosis secondary to vascular occlusion that appears to be partly mediated by

thromboxane A_2 release. The laser treatment induces a photochemical, not a thermal, effect. The necrotic reaction and associated inflammatory response evolve over several days.

Clinical efficacy

In a controlled clinical trial, a PhotoBarr PDT + OM (omeprazole) patient group (n=183) was compared to a group of patients receiving OM only (n=70). Eligible patients for this study were to have biopsy-proven HGD in Barrett's oesophagus (BO). Patients were excluded from the study if there was a presence of invasive oesophageal cancer, if they had a history of cancer other than non-melanoma skin cancer or if they had received prior PDT to the oesophagus. Other exclusion criteria were patients in whom omeprazole therapy was contraindicated.

Patients randomised to treatment with PDT received PhotoBarr at a dose of 2 mg/kg body weight through slow intravenous injection over 3 to 5 minutes. One or 2 laser light treatments were administered following PhotoBarr injection. The first laser light session occurred 40-50 hours after injection and a second session, if indicated, occurred 96-120 hours after injection. Co-administration of omeprazole (20 mg BID) began at least 2 days before PhotoBarr injection. Patients randomised to the OM only group received orally omeprazole 20 mg BID for the duration of the study.

Patients were followed every 3 months until 4 consecutive, quarterly follow-up endoscopic biopsy results were negative for HGD, and then biannually until the last enrolled patient had completed a minimum of 24 months of follow-up evaluations after randomisation.

PhotoBarr PDT + OM was effective in eliminating HGD in patients with BO. At final analysis, performed at a minimum of 24 months follow-up, a statistically significant percentage of patients (77%) in the PhotoBarr PDT + OM group demonstrated complete HGD ablation compared to 39% of patients in the OM alone group ($p<0.0001$). Fifty-two percent of patients in the PDT + OM group showed normal squamous cell epithelium while 59% had absence of dysplasia compared to 7% and 14% in the OM alone group, respectively ($p<0.0001$). These results confirm those observed after a minimum of 6 months follow-up which showed HGD ablation in 72% of patients in the PhotoBarr PDT + OM group compared to 31% in the OM only group. Forty-one percent of patients showed normal squamous cell epithelium and 49% had absence of dysplasia.

By the end of the minimum follow-up of two years, 13% in the PhotoBarr PDT + OM group had progressed to cancer compared to 28% in the OM only group in the intent-to-treat (ITT) population. The proportion of patients who progressed to cancer in the PhotoBarr PDT + OM group was statistically lower than in the OM only group ($p=0.0060$). The survival curves indicated that, by the end of the entire follow-up period, patients in the PhotoBarr PDT + OM group had a 83% chance of being cancer-free as compared to a 53% chance for patients in the OM only group. Comparison between the survival curves of the two treatment arms using the log rank test showed a statistically significant difference between the curves of the two groups in the ITT population ($p=0.0014$) indicating a significant delay in the progression to cancer.

5.2 Pharmacokinetic properties

The pharmacokinetics of porfimer sodium have been studied in 12 patients with endobronchial cancer and 23 healthy subjects (11 men and 12 women), given 2 mg/kg porfimer sodium through slow intravenous injection. Plasma samples were obtained up to 56 days (patients) or 36 days (volunteers) post injection.

In patients,the mean peak plasma concentration (C_{max}) was 79.6 µg/ml (C.V. 61%, range 39-222), whereas in volunteers C_{max} was 40 µg/ml and AUC_{inf} was 2400 µg/h/ml.

Distribution

In vitro binding of porfimer sodium to human serum protein is around 90% and independent of concentration between 20 and 100 µg/ml.

Elimination
Porfimer sodium is cleared slowly from the body, with a mean CL_T of 0.859 ml/h/kg (C.V. 53%) in patients.

The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The mean elimination half-life ($t_{1/2}$) was 21.5 days (CV 26 %, range 264-672) in patients and 17 days in volunteers.

Special populations
The influence of renal and hepatic impairment on exposure to porfimer sodium has not been evaluated (see sections 4.2, 4.3 and 4.4).

Gender had no effect on pharmacokinetic parameters except for t_{max}, which was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of porfimer sodium in men and women were very similar.

5.3 Preclinical safety data

Porfimer sodium was not mutagenic in standard genotoxicity tests in the absence of light. With light activation, porfimer sodium was mutagenic in some *in-vitro* tests.

Reproductive toxicology studies were insufficient to support the safety of porfimer sodium during pregnancy, as no light activation had been used. In these studies foetotoxicity, but not teratogenicity, occurred in rats and rabbits only at evaluated intravenous doses (greater than of equal to 4 mg/kg) and at greater frequency (daily) compared in the clinical use.

Preclinical studies indicate that the excretion of PhotoBarr components occurs primarily via the faecal route

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder: 3 years.

After reconstitution: use immediately (within 3 hours).

After it has been reconstituted, PhotoBarr should be used immediately (within 3 hours) and protected from light. Chemical and physical in-use stability has been demonstrated for 3 hours at 23°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton and vial after the EXP.

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

75 mg powder in a vial (glass type I, 40 ml capacity) with a grey butyl stopper.
Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution
PhotoBarr 75 mg vial should be reconstituted with 31.8 ml of 5% glucose solution for injection, resulting in a final porfimer sodium concentration of 2.5 mg/ml in the solution for injection.

Do not use other diluents. Do not mix PhotoBarr with other medicinal products in the same solution. Sufficient vials of PhotoBarr should be reconstituted to provide the patient with a dose of 2 mg/kg. For most patients (up to 75 kg) two vials of PhotoBarr 75 mg will suffice. A PhotoBarr 15 mg vial will be needed for every additional 7.5 kg body weight.

Spills and disposal
Spills of PhotoBarr should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended.

PhotoBarr is for single use only and any unused solution should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

Accidental exposure
PhotoBarr is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, PhotoBarr might be an eye and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic overdose, any accidentally overexposed person must be protected from bright light.'

7. MARKETING AUTHORISATION HOLDER

Pinnacle Biologics B.V.
p/a Trust Company Amsterdam B.V.
Crystal Tower 21st Floor,
Orlyplein 10, 1043 DP Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/272/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 March 2004
Date of latest renewal: 4 March 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Axcan Pharma SAS
Route de Bû
78550 Houdan
France

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall agree the details of educational materials with the National Competent Authorities to ensure that all health care professionals who intend to prescribe and/or dispense PhotoBarr are provided with the following:

- Prescriber guide
- Prescriber slide kit
- Healthcare professionals administration and monitoring guide
- Patient alert card
- Patient guide

The following *key elements* should be included in the educational materials:

Prescriber guide and Prescriber slide kit

- The educational tools are designed to aid physicians in optimising the benefit-risk ratio of porfimer treatment.
- Patients should NOT be treated with porfimer if:
  - they have severe hepatic disease.
  - they have trachea or broncho-oesophageal fistulas.
  - they have suspected erosions of major blood vessels.
- Caution should be exercised if patients have moderate hepatic disease
- Before initiating therapy,
  - The patient should be screened for skin type
  - Patients should be aware of the long half-life of porfimer and that the compound gets activated by light.
  - Patients should avoid being exposed to light for 60-90 days post-exposure.
  - all patients should know that UV blocking is not effective in blocking visible light which activates porfimer.
  - Patients should be aware of potential risk factors (skin phototype and hepatic impairment).
  - Patients should be instructed to seek medical advice if signs/symptoms suggestive of photosensitivity occur during or after therapy with porfimer.

Healthcare professionals administration and monitoring guide

- It is important to follow exactly the correct steps for reconstitution and administration of porfimer.
- It is important to have an appropriate light dose and a proper setting for the laser.
- Any unused product or waste material should be disposed of in accordance with local requirements.
- Healthcare professionals should be aware of side effects that may arise during or shortly after treatment, and how to treat them.
- Patients should be warned of the possibility of long term side effects, especially photosensitivity, and the need to seek medical assistance if they arise.
- Record the patient's skin type and the date of injection on the patient alert card

Patient alert card

- The need to show this card to any doctor treating them
- That PhotoBarr
  - Remains in your body for 60-90 days after receiving the injection
  - Is activated by visible light
  - There is an increased risk of photosensitivity (sensitivity to light)
  - Exposed skin will become red and cause discomfort in most cases but severe cases of photosensitivity are possible
  - Commercially available sun blocks are not effective in preventing sensitivity due to light
  - Photosensitivity can only be prevented by avoiding exposure to the sun for 90 days after receiving the PhotoBarr injection
- You should not be treated with PhotoBarr if you have severe liver disease (eg cirrhosis)
- You should be screened for skin type
- Area in card for physician to record skin type and date of injection.

Patient guide

- Brief background and introduction to Barrett's oesophagus and high grade dysplasia
- What photodynamic therapy is
- Patients should inform their doctor **before** they start treatment if they have severe hepatic disease.
- That PhotoBarr
  - Remains in your body for 60-90 days after receiving the injection
  - Is activated by visible light
  - There is an increased risk of photosensitivity (sensitivity to light)
  - Exposed skin will become red and cause discomfort in most cases but severe cases of photosensitivity are possible
  - Commercially available sun blocks are not effective in preventing sensitivity due to light
- Photosensitivity can only be prevented by avoiding exposure to the sun for 90 days after receiving the PhotoBarr injection
- It is important that patients tell their doctor if they get exposed to sunlight after receiving treatment with PhotoBarr.
- There are a number of potential side effects that patients should be aware of.

- **OTHER CONDITIONS**

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products of human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton - 15 mg

1. NAME OF THE MEDICINAL PRODUCT

PhotoBarr 15 mg powder for solution for injection
Porfimer sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 15 mg porfimer sodium. After reconstitution, each ml solution contains 2.5 mg porfimer sodium.

3. LIST OF EXCIPIENTS

Hydrochloric acid, sodium hydroxide (for pH adjustment).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.
After reconstitution, protect from light and use within 3 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pinnacle Biologics B.V.
p/a Trust Company Amsterdam B.V.
Crystal Tower 21st Floor,
Orlyplein 10, 1043 DP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/272/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 15 mg - 7 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PhotoBarr 15 mg powder for solution for injection
Porfimer sodium
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – 75 mg

1. NAME OF THE MEDICINAL PRODUCT

PhotoBarr 75 mg powder for solution for injection
Porfimer sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 75 mg porfimer sodium
After reconstitution, each ml solution contains 2.5 mg porfimer sodium.

3. LIST OF EXCIPIENTS

Hydrochloric acid, sodium hydroxide (for pH adjustment).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light
After reconstitution, protect from light and use immediately within 3 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pinnacle Biologics B.V.

p/a Trust Company Amsterdam B.V.
Crystal Tower 21st Floor,
Orlyplein 10, 1043 DP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/272/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 75 mg - 40 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PhotoBarr 75 mg powder for solution for injection
Porfimer sodium
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

75 mg

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

PhotoBarr 15 mg powder for solution for injection
Porfimer sodium

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again
- If you have any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PHOTOBARR IS AND WHAT IT IS USED FOR

PhotoBarr is a light-activated medicine used in photodynamic therapy (PDT) in combination with a non-burning red laser light. PDT specifically targets and destroys abnormal cells.

PhotoBarr is used to remove high-grade dysplasia (cells with atypical changes that increase the risk of developing cancer) in patients with Barrett's oesophagus (gullet).

2. BEFORE YOU USE PHOTOBARR

Do not use PhotoBarr
- if you are allergic (hypersensitive) to porfimer sodium, other porphyrins or any of the other ingredients of PhotoBarr (listed in section 6, '*What PhotoBarr contains'*)
- if you have porphyria
- if you have an opening (fistula) between the oesophagus and the airways
- if you suffer from varices of your oesophageal veins or erosion of other major blood vessels
- if you have ulcers in your oesophagus
- if you have severe liver or kidney problems

Take special care with PhotoBarr
Tell your doctor if any of the following applies to you:
- you are taking any other medicines (see below),
- you have a liver or kidney problems
- you have a family history of cataracts
- you are 75 years or older,
- you have or have had heart or lung disease

PhotoBarr should not be used in children and adolescents below 18 years of age, due to lack of experience.

Using other medicines
Tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription. Some other medicines may increase the risk for photosensitivity reactions for example antibiotics or antidiabetic medicines.

Using PhotoBarr with food and drink
The laser light application will induce difficulties with swallowing (pain, nausea and vomiting). Therefore, you should take liquid food only for a few days (in some cases up to 4 weeks).
If eating or drinking becomes impossible or if you keep vomiting, please return to the clinical for medical attention.

Pregnancy and breast-feeding
PhotoBarr should not be used during pregnancy unless clearly necessary.
Women of childbearing age should take adequate contraceptive precautions whilst and up to 90 days after receiving PhotoBarr.

You should stop breast-feeding before using PhotoBarr.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.
During your light treatment you may receive sedation. In this case, you should avoid any activities that require mental alertness such as driving a car or using any machine.

3. HOW TO USE PHOTOBARR

How does photodynamic therapy (PDT) work?
One course of PDT consists of one injection of PhotoBarr plus one or two laser light applications.
To increase your response rate, you may need up to three PDT courses, separated by at least 90 days.

PhotoBarr injection: You will receive one intravenous injection of PhotoBarr (2 mg per kg of body weight), 40 to 50 hours before laser light treatment. The reddish-brown solution is slowly injected, over 3 to 5 minutes, into a vein.

Laser light treatment: Your doctor will apply the red laser light (not a burning laser) to the involved area using an endoscope (a device used to see inside certain parts of the body). You may receive a second laser light treatment 96-120 hours after the initial injection of PhotoBarr.
You will be given a sedative along with a local anaesthetic to minimise discomfort.

If you miss the laser light treatment
Both the medicine and laser light are necessary for the therapy to work. If you realise that you have missed your appointment for the laser treatment, contact your doctor immediately. Your doctor will decide how to proceed with the treatment.

How to prevent a photosensitivity reaction
Photosensitivity reactions are very common side effects of PhotoBarr (affecting more than 2 users in 3). They consist mainly of sunburn-like reactions, mild redness on exposed skin, usually the face and hands. For **90 days** following your PhotoBarr injection, you must take precautions to avoid exposure of skin and eyes to light. If you have liver problems, this period might be longer.

Since PhotoBarr is activated by the red part of light, sunscreens for UV (ultraviolet) light will not protect you against photosensitivity reactions.

Direct sunlight:
Before you go to receive your PhotoBarr injection, check that there are adequate shades and curtains in your home to keep out bright sunlight. If you go out during daylight hours (even on cloudy days and while travelling in a vehicle), you should take the following precautions:
- cover as much skin as possible by wearing a long-sleeved shirt, trousers, socks, shoes, gloves and a wide brimmed hat
- protect your eyes with dark sunglasses.
- remember to take protective clothing and sunglasses with you to your appointment, as you will be photosensitive once the injection has been given.

Indoor light:
Avoid direct exposure to bright indoor lights, including dental lamps, operating room lamps, unshaded light bulbs at close proximity or neon lights.
However, to speed up the natural process of inactivating the medicine in your body, it is good to expose the skin to normal levels of indoor light. You do not need to stay in a darkened room.

Photosensitivity skin test

About 90 days after the PhotoBarr injection, you should test the photosensitivity of your skin as follows:

Cut a 2-inch hole in a paper bag, put it on your hand or elbow (not your face).

Expose a small area of skin to sunlight for 10 minutes.

Check for the appearance of red marks, swelling or blistering after one day.

- if none of these appear on the exposed area, then you can gradually return to your normal outdoor activities, limiting exposure to the sun during the midday hours.
- if any of these signs are seen, then continue to protect yourself from bright light for 2 more weeks, then repeat the skin test.

If you go on holiday to an area with more sunshine, remember to repeat the skin test, especially if some areas of skin have not been exposed to sunlight since your PhotoBarr treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PhotoBarr can cause side effects, although not everybody gets them.

All patients who receive PhotoBarr will be photosensitive (sensitive to light) and must observe precautions to avoid direct sunlight and bright indoor light (see above '*How to prevent a photosensitivity reaction*').

Tell your doctor **immediately**:
- if you notice a change in your eyesight. You should visit your eye specialist.
- if you are not able to swallow at all or repeated vomiting occurs

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data.

Very common side effects

- fever
- photosensitivity reactions (see section 3)
- vomiting, nausea
- tightening of the gullet (oesophagus), difficulty in swallowing that may cause pain
- constipation, dehydration

Common side effects

- back pain, pain in arms and legs, pain due to treatment
- headache, feeling nervous, tingling feeling, problems sleeping
- abdominal stiffness, stomach pain, vomiting blood
- disorders of the gullet such as ulcer, irritation or constriction
- loose stools, passing dark tarry stool, sore throat, hiccups, belching
- fluid in chest, chest pain, fast heart beat, shortness of breath, shakes due to high fever, chills
- loss of weight, decrease in appetite, feeling tired, loss of taste
- skin ulcer, rash, itchiness, hives, change in skin colour, scratch, scar, abnormal tissue, bump on the skin, very small cysts in the skin, dry and fragile skin

Uncommon side effects

- difficulty breathing, decrease in level of oxygen, choking, swelling of the airways, fluid in airways, shortness of breath during physical activity, wheezing, coughing up more phlegm, coughing up blood, stuffy nose
- lung infection, sinus infection
- chest pain or heart attack, high blood pressure or low blood pressure, chest discomfort
- abnormal blood test results, including increase in white blood cells, low potassium levels
- bleeding, loss of blood, increased tendency to bruise
- over development of breasts in men, inability to urinate, temperature intolerance, cold sweats, night sweats
- general swelling, general pain, musculoskeletal chest pain, stiffness of joint, inflammation of the heel
- shakes, restlessness, dizziness, numbness, flushes, feeling weak, feeling unwell
- loss of hearing, ringing in the ears, swelling of the eye, eye pain
- rash, redness at the injection site, nail fungal infection, skin infection, blister, itchy skin, overgrowth of tissue at the site of skin injury, scar pain, scab, presence of skin moles, abnormal hair growth

Frequency not known side effects

- lung infection
- lower number of red cells in your blood
- cataract
- lesion in intestine, abnormal opening between the wind pipe and the food pipe
- allergic reaction
- blood clots in your vessels, blockage of blood arteries, inflammation of a vein

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PHOTOBARR

Keep out of the reach and sight of children.

Do not use PhotoBarr after the expiry date which is stated on the carton and vial after EXP.

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.

After reconstitution, PhotoBarr solution should be protected from light and used immediately (within 3 hours). Chemical and physical in-use stability has been demonstrated for 3 hours at 23°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

6. FURTHER INFORMATION

What PhotoBarr contains
- The active substance is porfimer sodium. Each vial contains 15 mg of porfimer sodium. After reconstitution, each ml solution contains 2.5 mg porfimer sodium.
- The other ingredients are hydrochloric acid and sodium hydroxide (for pH adjustment).

What PhotoBarr looks like and contents of the pack
PhotoBarr is a reddish brown powder for solution for injection.
One single-use vial per pack.

Marketing Authorisation Holder
Pinnacle Biologics B.V., p/a Trust Company Amsterdam B.V., Crystal Tower 21st Floor, Orlyplein 10, 1043 DP Amsterdam, The Netherlands

Manufacturer
Axcan Pharma SAS, Route de Bû, 78550 Houdan, France

This leaflet was last approved in

For any information about this medicine, please contact the Marketing Authorisation Holder.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

PhotoBarr 75 mg powder for solution for injection
Porfimer sodium

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again
- If you have any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PHOTOBARR IS AND WHAT IT IS USED FOR

PhotoBarr is a light-activated medicine used photodynamic therapy (PDT)in combination with a non-burning, red laser light. PDT specifically targets and destroys abnormal cells.
PhotoBarr is used to remove high-grade dysplasia (cells with atypical changes that increase the risk of developing cancer) in patients with Barrett's oesophagus (gullet).

2. BEFORE YOU USE PHOTOBARR

Do not use PhotoBarr

- if you are allergic (hypersensitive) to porfimer sodium other porphyrins or to any other ingredients of PhotoBarr (listed in section 6 "W*hat PhotoBarr contains"*)
- if you have porphyria
- if you have an opening (fistula) between the oesophagus and the airways
- if you suffer from varices of your oesophageal veins or erosion of other major blood vessels
- if you have ulcers in your oesophagus
- if you have severe liver of kidney problems

Take special care with PhotoBarr
Tell your doctor if any of the following applies to you:
- you are taking any other medicines (see below),
- you have liver or kidney problems
- you have a family history of cataracts,
- you are 75 years or older,
- have or have had heart or lung disease

Using other medicines
Tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription. Some other medicines may increase the risk for photosensitivity reactions for example antibiotics or antidiabetic medicines.

Using PhotoBarr with food and drink
The laser light application will induce difficulties with swallowing (pain, nausea and vomiting). Therefore, you should take liquid food only for a few days (in some cases up to 4 weeks).

If eating or drinking becomes impossible or if you keep vomiting, please return to the clinical for medical attention.

Pregnancy and breast-feeding
PhotoBarr should not be used during pregnancy unless clearly necessary.
Women of childbearing age should take adequate contraceptive precautions whilst and up to 90 days after receiving PhotoBarr.

You should stop breast-feeding before using PhotoBarr.

Driving and using machines:
No studies on the effects on the ability to drive and use machines have been performed.
During your light treatment you may receive sedation. In this case, you should avoid any activity that requires mental alertness such as driving a car or using any machine.

3. HOW TO USE PHOTOBARR

How does photodynamic therapy (PDT) work?

One course of PDT consists of one injection of PhotoBarr plus one or two laser light applications. To increase your response rate, you may need up to three PDT courses, separated by at least 90 days.

PhotoBarr injection: You will receive one intravenous injection of PhotoBarr (2 mg per kg of body weight) 40 to 50 hours before laser light treatment. The reddish-brown solution is slowly injected, over 3 to 5 minutes, into a vein.

Laser light treatment: Your doctor will apply the red laser light(not a burning laser) to the involved area using an endoscope (a device used to see inside certain parts of the body).. You may receive a second laser light treatment 96-120 hours after the initial injection of PhotoBarr. You will be given a sedative along with a local anaesthetic, to minimise discomfort

If you miss the laser light treatment
Both the medicine and laser light are necessary for the therapy to work. If you realise that you have missed your appointment for the laser treatment, contact your doctor immediately. Your doctor will decide how to proceed with the treatment.

How to prevent a photosensitivity reaction
Photosensitivity reactions are very common side effects of PhotoBarr (affecting more than 2 users in 3). They consist mainly of sunburn-like reactions, mild redness on exposed skin, usually the face and hands. For **90 days** following your PhotoBarr injection, you must take precautions to avoid exposure of skin and eyes to light. If you have liver problems, this period might be longer.

Since PhotoBarr is activated by the red part of light, sunscreens for UV (ultraviolet) light will not protect you against photosensitivity reactions.

Direct sunlight:
Before you go to receive your PhotoBarr injection, check that there are adequate shades and curtains in your home to keep out bright sunlight. If you go out during daylight hours (even on cloudy days and while travelling in a vehicle), you should take the following precautions:

- cover as much skin as possible by wearing a long-sleeved shirt, trousers, socks, shoes, gloves and a wide brimmed hat
- protect your eyes with dark sunglasses.
- remember to take protective clothing and sunglasses with you to your appointment, as you will be photosensitive once the injection has been given.

Indoor light:
Avoid direct exposure to bright indoor lights, including dental lamps, operating room lamps, unshaded light bulbs at close proximity or neon lights.
However, to speed up the natural process of inactivating the medicine in your body, it is good to expose the skin to normal levels of indoor light. You do not need to stay in a darkened room.

Photosensitivity skin test

About 90 days after the PhotoBarr injection, you should test the photosensitivity of your skin as follows:

Cut a 2-inch hole in a paper bag, put it on your hand or elbow (not your face).

Expose a small area of skin to sunlight for 10 minutes.

Check for the appearance of red marks, swelling or blistering after one day.

- if none of these appear on the exposed area, then you can gradually return to your normal outdoor activities, limiting exposure to the sun during the midday hours.
- if any of these signs are seen, then continue to protect yourself from bright light for 2 more weeks, then repeat the skin test.

If you go on holiday to an area with more sunshine, remember to repeat the skin test, especially if some areas of skin have not been exposed to sunlight since your PhotoBarr treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PhotoBarr can cause side effects, although not everybody gets them.

All patients who receive PhotoBarr will be photosensitive (sensitive to light) and must observe precautions to avoid direct sunlight and bright indoor light (see above '*How to prevent a photosensitivity reaction'*).

Tell your doctor **immediately**:
- if you notice a change in your eyesight. You should visit your eye specialist.
- if you are not able to swallow at all or repeated vomiting occurs

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data.

Very common side effects

- fever
- photosensitivity reactions (see section 3)
- vomiting, nausea
- tightening of the gullet (oesophagus), difficulty in swallowing that may cause pain
- constipation, dehydration

Common side effects

- back pain, pain in arms and legs, pain due to treatment
- headache, feeling nervous, tingling feeling, problems sleeping
- abdominal stiffness, stomach pain, vomiting blood
- disorders of the gullet such as ulcer, irritation or constriction
- loose stools, passing dark tarry stool, sore throat, hiccups, belching
- fluid in chest, chest pain, fast heart beat, shortness of breath, shakes due to high fever, chills
- loss of weight, decrease in appetite, feeling tired, loss of taste
- skin ulcer, rash, itchiness, hives, change in skin colour, scratch, scar, abnormal tissue, bump on the skin, very small cysts in the skin, dry and fragile skin

Uncommon side effects

- difficulty breathing, decrease in level of oxygen, choking, swelling of the airways, fluid in airways, shortness of breath during physical activity, wheezing, coughing up more phlegm, coughing up blood, stuffy nose
- lung infection, sinus infection
- chest pain or heart attack, high blood pressure or low blood pressure, chest discomfort
- abnormal blood test results, including increase in white blood cells, low potassium levels
- bleeding, loss of blood, increased tendency to bruise
- over development of breasts in men, inability to urinate, temperature intolerance, cold sweats, night sweats
- general swelling, general pain, musculoskeletal chest pain, stiffness of joint, inflammation of the heel
- shakes, restlessness, dizziness, numbness, flushes, feeling weak, feeling unwell
- loss of hearing, ringing in the ears, swelling of the eye, eye pain
- rash, redness at the injection site, nail fungal infection, skin infection, blister, itchy skin, overgrowth of tissue at the site of skin injury, scar pain, scab, presence of skin moles, abnormal hair growth

Frequency not known side effects

- lung infection
- lower number of red cells in your blood
- cataract
- lesion in intestine, abnormal opening between the wind pipe and the food pipe
- allergic reaction
- blood clots in your vessels, blockage of blood arteries, inflammation of a vein

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PHOTOBARR

Keep out of the reach and sight of children.

Do not use PhotoBarr after the expiry date which is stated on the carton and vial after EXP.

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.

After reconstitution, PhotoBarr solution should be protected from light and used immediately (within 3 hours). Chemical and physical in-use stability has been demonstrated for 3 hours at 23°C. From a

microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

6. FURTHER INFORMATION

What PhotoBarr contains

- The active substance is porfimer sodium. Each vial contains 75 mg of porfimer sodium. After reconstitution, each ml solution contains 2.5 mg porfimer sodium.
- The other ingredients are hydrochloric acid and/or sodium hydroxide (for pH adjustment).

What PhotoBarr looks like and contents of the pack

PhotoBarr is a reddish brown powder for solution for injection.
One single-use vial per pack.

Marketing Authorisation Holder

Pinnacle Biologics B.V., p/a Trust Company Amsterdam B.V., Crystal Tower 21st Floor, Orlyplein 10, 1043 DP Amsterdam, The Netherlands

Manufacturer

Axcan Pharma SAS, Route de Bû, 78550 Houdan, France

This leaflet was last approved in

For any information about this medicine, please contact the Marketing Authorisation Holder.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.